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# Diagnosis and Management of fungi difficult to treat

## Current trends and future perspectives in infections due to emerging yeasts and molds difficult to treat

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# Disclosures

- Merck
- Pfizer
- Gador
- Raffo
- Ivax/Teva
- Biodiagnóstico

# Emerging yeasts and molds

- Yeast

- *Candida albicans* (R)
- *Candida glabrata* (R)
- ~~• *Candida auris*~~
- *Trichosporon* sp

- Molds (hyaline)

- ~~*Aspergillus fumigatus* (R)~~
- *Non Aspergillus fumigatus*
- ~~• *Fusarium* sp~~
- *Scedosporium* sp
- *Paecilomyces* sp
- *Acremonium* sp
- *Scopulariopsis* sp

- Molds (pigmentate)

- *Alternaria* sp
- *Exserohilum* sp
- *Curvularia* sp
- *Aureobasidium* sp
- *Cladophialophora* sp
- *Exophiala* sp
- *Ochroconis* sp

- Molds (cenocitic)

- *Lichtheimia* sp
- *Rhizopus* sp
- *Mucor* sp

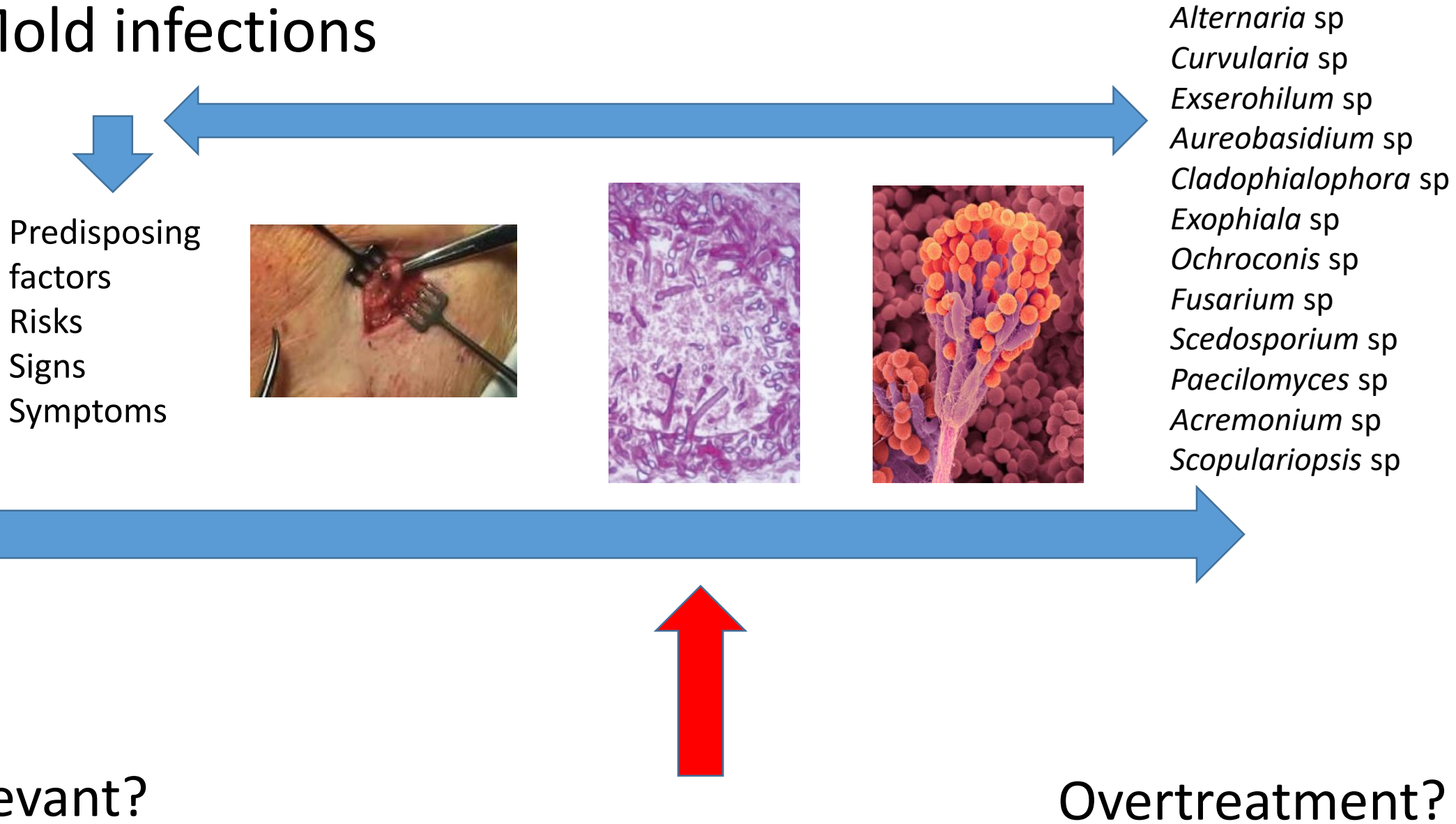
- Dimorphic

- *Sporothrix* sp
- *Paracoccidioides* sp

# Introduction

- Invasive fungal infections (IFIs) are associated with increased morbidity and unacceptably high mortality among patients with underline conditions.
- Treatment options are limited, including only four chemical classes: polyenes, triazoles, echinocandins and flucytosine.
- The expansion of the use of antifungal agents over the last two decades contributed to the development of antifungal resistance:
  - Hospital environment.
  - Agricultural and industrial fungicides.
  - Household environment.

# Mold infections



# *Trichosporon*

- Is the third most commonly isolated noncandidal yeast from clinical specimens .
- Is the second most common cause of yeast fungaemia in patients with malignant haematological disease.
- Can be found in:
  - Soil and fresh water
  - Normal biota (human skin and gastrointestinal tract)
- Infection can be superficial, subcutaneous or systemic.
- Aetiological agents
  - *Trichosporon asahii*
  - *Trichosporon asteroides*
  - *Trichosporon cutaneum*
  - *Trichosporon inkin*
  - *Trichosporon mucoides*
  - *Trichosporon ovoides*.

# *Trichosporon*

	<b>Azole</b>		<b>Polyenes</b>	<b>Echinocandin</b>
	Fluconazole	Voriconazole	Amphotericin B	
<b><i>T. asahii</i></b>	Low activity	Susceptible	Resistant	Resistant
<b><i>T. cutaneum</i></b>	Low activity	Low activity	Resistant	Resistant

- *T. mucoides*, *T. inkin*, and *T. ovoides* seem to be much more susceptible to fluconazole than are *T. asahii*.

# Non *Aspergillus fumigatus*

	<b>Inherent resistance</b>	<b>Acquired resistance</b>
<b><i>Asp. calidoustus</i></b>	FCZ, AMB	VCZ, ISV
<b><i>Asp. lentulus</i></b>	FCZ, AMB	VCZ, ISV
<b><i>Asp. terreus</i></b>	FCZ, AMB	VCZ, ISV
<b><i>Asp. flavus</i></b>	FCZ, AMB	VCZ, ISV
<b><i>Asp. nidulans</i></b>	FCZ, AMB	VCZ, ISV



# TRANSNET

**No. (%) of Invasive Fungal Infection (IFI) Cases in the Surveillance Cohort, by Transplant**

**Type**

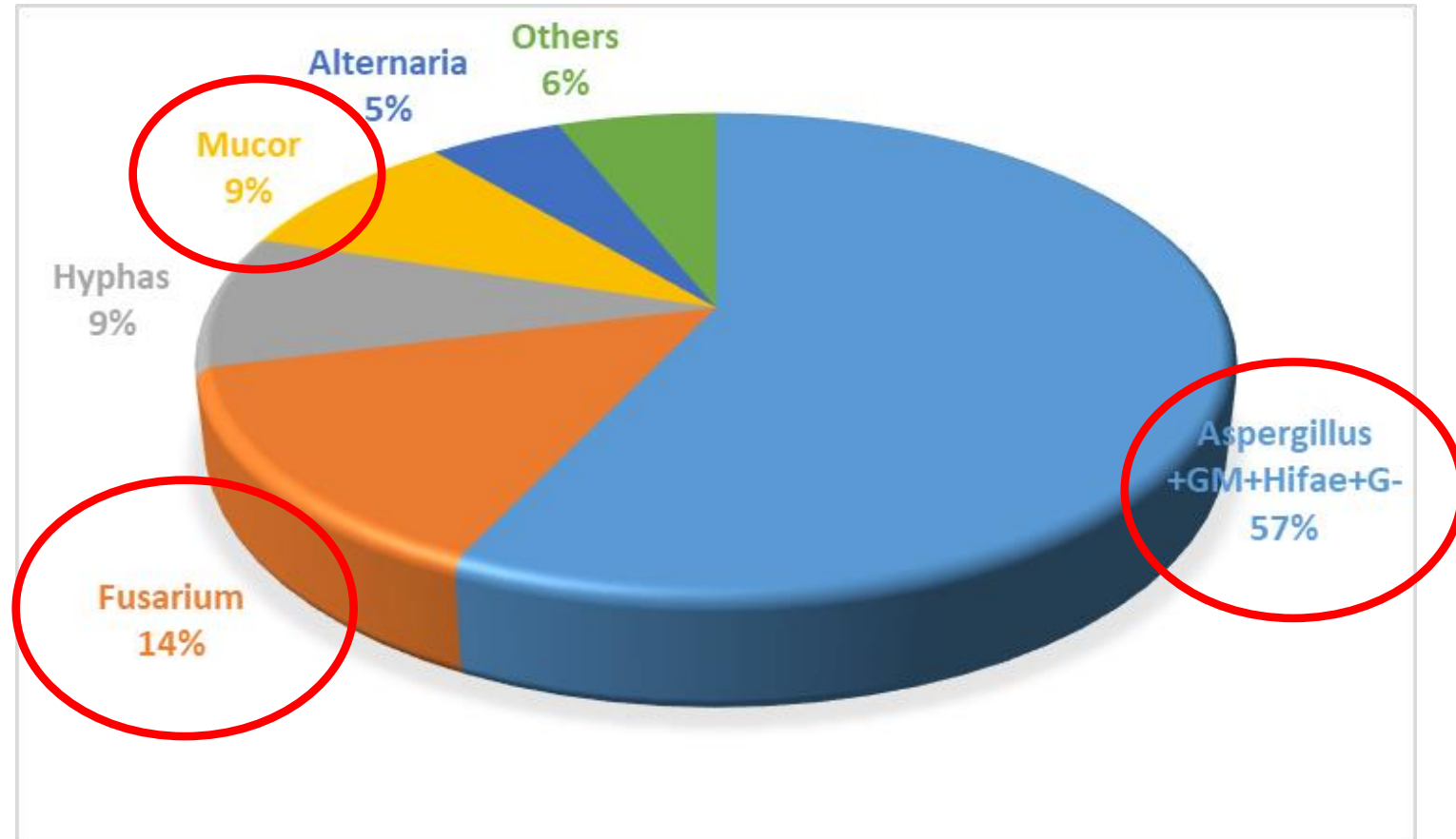
IFI type	Kidney ( <i>n</i> = 332)	Liver ( <i>n</i> = 378)	Pancreas ( <i>n</i> = 128)	Lung ( <i>n</i> = 248)	Heart ( <i>n</i> = 99)	Small bowel ( <i>n</i> = 22)
Candidiasis	164 (49)	255 (68)	97 (76)	56 (23)	48 (49)	19 (85)
Aspergillosis	47 (14)	42 (11)	6 (5)	109 (44)	23 (23)	0 (0)
Zygomycosis	8 (2)	9 (2)	0 (0)	8 (3)	3 (3)	0 (0)
Other mold	10 (3.0)	9 (2.4)	4 (3.1)	49 (19.8)	7 (7.1)	0 (0.0)
Unspecified mold	7 (2.1)	8 (2.1)	0 (0.0)	7 (2.8)	2 (2.0)	0 (0.0)
Cryptococcosis	49 (15)	24 (6)	6 (5)	6 (2)	10 (10)	1 (5)
Endemic mycoses	33 (10)	17 (5)	8 (6)	3 (1)	3 (3)	0 (0)
Pneumocystosis	5 (1)	0 (0)	1 (1)	4 (2)	3 (3)	0 (0)
Other yeast	6 (1.8)	9 (2.4)	5 (3.9)	0 (0.0)	0 (0.0)	1 (5)
Unspecified yeast	3 (0.9)	5 (1.3)	1 (0.8)	6 (2.4)	0 (0.0)	1 (5)



## INVASIVE MOLD DISEASE (IMD) IN IMMUNOCOMPROMISED (IC) NON-HIV Patients (pts): PRELIMINARY DATA FROM THE FIRST ARGENTINEAN REGISTRY FOR INVASIVE MYCOSES (REMIIN).

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# Mucormycosis

- Common part of the general environment.
- Uncontrolled diabetes.
- Hematologic malignancies
  - Neutropenia
  - HSCT
  - Median time from diagnosis: 8.8 months.
- The most common sites of involvement:
  - Sinuses
  - Pulmonary
  - Skin
  - Gastrointestinal

Clin Microbiol Infect. 2014 Apr;20 Suppl 3:5-26.

Mycoses. 2014 Dec;57 Suppl 3:2-7

Semin Respir Crit Care Med. 2015

Clin Chest Med. 2017 Sep;38(3):555-573

# Mucormycosis

- Imaging
  - CT
    - Reverse Halo signs or atoll sign.
    - Halo signs.
- Microbiology
  - Direct examination
  - Culture
  - Molecular methods

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# Mucormycosis

	<b>AMB</b>	<b>POS</b>	<b>CAN</b>	<b>FCZ</b>	<b>ITC</b>	<b>VCZ</b>	<b>TBF</b>	<b>5FC</b>
<b><i>Lichtheimia</i></b>	S	S	R	R	S-R	R	S	R
<b><i>Rhizopus</i></b>	S	S	R	R	S-R	R	S-R	R
<b><i>Mucor</i></b>	S	S-R	R	R	S-R	R	S-R	R

- L-AMB (10 mg/kg/d)
- Surgery
- Posaconazole
- Isavuconazole
- Hyperbaric oxygen.
- Granulocyte infusion
- Granulocyte colony-stimulating factor (G-CSF)
- Combination:
  - Salvage Therapy.

# *Scedosporium* infections

- Isolated from:
  - Rural soils.
  - Polluted waters.
  - Composts.
- Saprophytes.
- Opportunistic infections in immunocompromised patients.
- Disseminated infections (CNS).
- Healthy individuals:
  - Near drowning accidents.
- Diagnosis:
  - Similar to aspergillosis.
  - Laboratory diagnosis:
    - Conventional methods such as culture, direct microscopy and histopathology.
    - Molecular-based identification methods.
    - Blood cultures may be positive in >50%.

# *Scedosporium* infections

	<b>AMB</b>	<b>5FC</b>	<b>Cand</b>	<b>FCZ</b>	<b>ITC</b>	<b>VCZ</b>	<b>POS</b>
<i>S. apiospermum</i>	I-R	R	R	R	S-R	S	S
<i>S. boydii</i>	I-R	R	R	R	S-R	S	S
<i>S. aurantiacum</i>	R	R	R	R	R	S	S-R
<i>S. prolificans</i>	R	R	I-R	R	R	R	R

- Voriconazole represents the first-line treatment.
- Surgical resection (localized lesion)
- *S. prolificans*:
  - Voriconazole plus terbinafine.
  - Sequential azole and terbinafine.
  - Voriconazole and caspofungin

# *Paecilomyces* infections

- Rarely pathogenic in humans.
- Isolated from soil and decaying plant material.
- Disseminated infection.
- Pneumonia.
- Cellulitis, fungaemia and pyelonephritis have been reported in immunosuppressed patients.
- *P. lilacinum* are highly resistant to amphotericin B
- *P. variotii* is usually amphotericin B susceptible.



# Alternariosis

- *Genus Alternaria*
  - *alternata*
  - *infectoria*
  - *tenuissima*
  - *alternatum*
  - *tenuis*
- Plant pathogen and is commonly isolated from soil, air and plants.
- Cutaneous or subcutaneous lesions mainly in immunosuppressed individuals.
- Sinusitis, keratitis.
- Allergic bronchopulmonary mycosis.
- Disseminated infections occur with painless papulo-nodular lesions or cutaneous nodules.
- Treatment
  - AMB
  - Itraconazole, Posaconazole, Terbinafine.

# *Exserohilum* infections

- *Exserohilum rostratum*
- Rare clinically significant pathogen causing invasive infections mainly in immunocompromised patients.
- Immunocompetent individuals usually after accidental inoculation.
- Fungal meningitis outbreak that was traced back to contaminated steroid injections.
  - 718 cases of fungal meningitis, and/or spinal or paraspinal.
  - 33 cases of peripheral joint infections.
  - 64 deaths.
- Voriconazole, Itraconazole, AMB

Clin Chest Med. 2017 Sep;38(3):555-573.

Clin Microbiol Infect. 2014 Apr;20 Suppl 3:47-75

# Sporotrichosis

- Genus Sporothrix
  - *S. brasiliensis*
  - *S. schenckii*
  - *S. globosa*
  - *S. luriei*
  - *S. pallida*
  - *S. candida*
  - *S. inflata*
  - *S. gossypina*
  - *S. stenoceras*
- Thermodimorphic fungi
- Cases of sporotrichosis have significantly increased in Brazil over the past decade.
- Zoonotic transmission.

# Sporotrichosis

- **Skin**

- **Lymphocutaneous**
- **Fixed cutaneous**
- **Multiple inoculation**

- Mucous membrane

- Ocular
- Nasal

- Systemic

- Osteoarticular
- Cutaneous disseminated
- Pulmonary
- Neurological

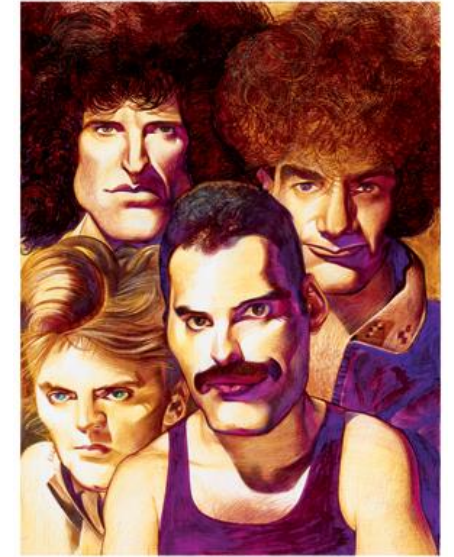
- Laboratory diagnosis

- Mycology

- Direct microscopy :“cigar-shaped” .
- **Isolation and the identification of the *Sporothrix* species.**
- Immunoelectrophoresis, agglutination, and immunodiffusion.
- **ELISA (Ss Con A-Binding Fraction) and Western blotting.**
- Molecular methods.

- Treatment

- Itraconazole, potassium iodide, terbinafine, and amphotericin B.



- *Pichia kudriavzevii*
- *Meyerozyma guilliermondii*
- *Lomentospora prolificans*
- *Purpureocillium lilacinum*

- *Candida krusei*
- *Candida guilliermondii*
- *Scedosporium prolificans*
- *Paecilomyces lilacinum*



Vintage's names

# Future Research Direction

- Development and implementation of laboratory diagnostic tools
  - Current technology does not allow rapid species identification or assessment of resistance.
  - New molecular technologies for the prompt and accurate detection of genes and mutations associated with fungal resistance are urgently needed.
- The existing antifungal agents are not sufficient.
- Limited antifungal armamentarium should be enriched with agents with novel mechanisms of action.